workplace. The Patent Office has recognized the utility and commercial value of libraries of agents, and may such libraries have been patented.

A claimed invention must have a specific and substantial utility. This requirement excludes "throw-away," "insubstantial," or "nonspecific" utilities, such as the use of a complex invention as landfill, as a way of satisfying the utility requirement of 35 U.S.C. 101. The presently claimed invention meets such requirements, because the claimed library provides a means of screening for randomized bioactive agents, and is specifically useful in the methods of the invention.

A rejection based on lack of utility should not be maintained if an asserted utility for the claimed invention would be considered specific, substantial, and credible by a person of ordinary skill in the art in view of all evidence of record. Office personnel are reminded that they must treat as true a statement of fact made by an applicant in relation to an asserted utility, unless countervailing evidence can be provided that shows that one of ordinary skill in the art would have a legitimate basis to doubt the credibility of such a statement.

In view of the above amendments and remarks, withdrawal of the rejection under 35 U.S. 101 is respectfully requested.

Claims 16-31 have been rejected under 35 U.S.C. 112, second paragraph. The claims have been amended to clarify the subject matter, and are respectfully submitted to meet the requirements of 35 U.S.C. 112.

Claims 16 and 21 have been rejected as indefinite in the recitation of the term "encoding", which is said to be more appropriate for a method claim than for a composition claim. Without conceding to the correctness of the rejection, the claim language has been amended to recite "that encodes" which language clearly refers to a nucleic acid, which is translated into the corresponding peptide or protein.

The antecedent basis for "said plurality" in claims 17-20 has been corrected.

Claims 23-25 and 30 have further been amended to clarify that in these claims the retroviral nucleic acid sequences further encode a fusion partner, which is translationally fused to the sequence encoding the candidate bioactive peptide. Such a genetic construct is supported in the specification, for example on page 37, line 19 and page 78, line 1. The specification further provides ample description of suitable fusion partners. For example, see page 6, lines 1-15,

> By "fusion partner" or "functional group" herein is meant a sequence that is associated with the candidate bioactive agent, that confers upon all members of the library in that class a common function or ability. Fusion partners can be heterologous (i.e. not native to the host cell), or synthetic (not native to any cell). Suitable fusion partners include, but are not limited to: a) presentation structures, as defined below, which provide the candidate bioactive agents in a conformationally restricted or stable form; b) targeting sequences, defined below, which allow the localization of the candidate bioactive agent into a subcellular or extracellular

compartment; c) rescue sequences as defined below, which allow the purification or isolation of either the candidate bioactive agents or the nucleic acids encoding them; d) stability sequences, which confer stability or protection from degradation to the candidate bioactive agent or the nucleic acid encoding it, for example resistance to proteolytic degradation; e) dimerization sequences, to allow for peptide dimerization; or f) any combination of a), b), c), d), and e), as well as linker sequences as needed.

Claims 30-31 have been amended to clarify that the candidate bioactive peptide is intracellular, and translationally fused to a fusion partner, for example as described above.

In view of the above amendments and remarks, Applicants respectfully submit that the presently claimed invention meets the requirements of 35 U.S.C. 112. Withdrawal of the rejection is requested.

Claims 16-31 have been provisionally rejected under the judicially created doctrine of obviousness type double patenting over Claims 47-50, and 53 of co-pending application no. 09/918,601 or claims 23-26 and 31-38 of copending application no. 09/727,715. Applicants respectfully submit that a provisional rejection of this type is properly addressed by allowance of one application, in the absence of other outstanding rejections, at which time a determination of double-patenting can be made based on the issued claims.

The Office Action states that Applicants are not entitled to their priority date because specification does not teach or enable fusion protein containing GFP reporter. Applicants respectfully draw the Examiner's attention to the issued patent U.S. 6,153,380, to which the present application claims priority. The patent states at column 52, line 42 "We will incorporate in the place of luciferase either the lacZ or GFP cDNAs for FACS-based assay", thereby describing the interchangeable use of luciferase, LacZ and GFP. Example 4 in the present application is also present in the priority application, and discloses the fusion of the reporter gene to the candidate bioactive peptide.

Claims 16-31 have been rejected under 35 U.S.C. 102 as anticipated by Jenkins *et al.* (1995) EMBO J. Jenkins reports combining retroviral expression cloning with random mutagenesis to identify two activating point mutations in the common signal-transducing subunit (h beta c) of the receptors for human granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin IL-3 and IL-5 by virtue of their ability to confer factor independence on the hematopoietic cell line, FDC-P1.

Applicants respectfully submit that the presently claimed invention is not anticipated by Jenkins. The present claims recite retroviral nucleic acid sequences that comprise an insertion of a

nucleic acid sequence that encodes a candidate bioactive peptide of from 4 to 100 amino acids in length comprising a randomized portion. Jenkins *et al.* disclose point mutations in a specific sequence. As is known in the art, point mutations are single nucleotide changes, and therefore do not teach or suggest insertions of sequences encoding peptides from 4 to 100 amino acids in length.

In view of the above amendments and remarks, Applicants respectfully submit that the presently claimed invention meets the requirements of 35 U.S.C. 102. Withdrawal of the rejection is requested.

Claims 16-24 and 29 have been rejected under 35 U.S.C. 102 as anticipated by Whitehead *et al.* (1995). Whitehead *et al.* describes a method of expression cloning of cDNAs, by inserting cDNAs into retroviral expression libraries. The office action points to page 709, first column. The reference states that "Some of the cDNAs described . . . appear to have acquired transforming activity via mutations arising in the process of cDNA library construction, i.e. truncation or inversion."

As discussed above with respect to Jenkins, the present claims recite an insertion of sequences encoding a randomized peptide of from 4 to 100 amino acids in length. The mutations described by Whitehead *et al.*, of truncations or inversions, do not provide for such a randomized amino acid sequence. A truncation would result in the deletion of a randomized sequence. And an inversion would result in a reversed sequence.

Further, the entire polypeptides described by Whitehead *et al.* are much large than the candidate bioactive peptides taught by Applicants. The sequences of Whitehead *et al.* methods are cDNAs. As shown in Table 2 and in Table 3, the size of the inserts range from a minimum of 800 bp to a maximum of 2800 bp. A cDNA insert of this size would encode a protein of from 266 to 933 amino acids, which is clearly well outside the size of the peptides recited in the present claims.

Applicants respectfully submit that the present invention is not anticipated by Whitehead *et al.* Withdrawal of the rejection is requested.

Claims 16-24, 29-30 have been rejected under 35 U.S.C. 102 as anticipated by Pan et al. (1995). Applicants respectfully submit that Pan *et al.* does not anticipate the presently claimed invention. The library of Pan *et al.* is an RNA library, where the RNA acts directly to bind to, or inactivate infectious particles. As stated in the abstract of the reference, "RNA and ribonuclease-resistant RNA analogs that bound and neutralyzed Rous Sarcoma Virus were isolated from a large pool of random sequences". The RNA does not provide coding sequences, and therefore could not encode a bioactive peptide. The reference fails to disclose retroviral vector sequences, regulatory

sequences for the expression of the randomized sequence, or peptides encoded by the randomized sequence. Withdrawal of the rejection is requested.

Claims 23-27 and 30-31 have been rejected under 35 U.S.C. 103 as unpatentable over any one of Jenkins *et al.*, Whitehead *et al.*, or Pan *et al.*, further in view of Nilsson *et al.* Applicants respectfully submit that the claimed invention is not taught or suggested by the cited combination of references. As discussed above, the library of the subject application differs from the genetic constructs described by the prior art references. The references collectively fail to adequately disclose a library of retroviral nucleic acid sequences comprising an introduced sequence that encodes a peptide of 4 to 100 amino acids having a randomized portion.

The secondary reference does not remedy the deficiencies of the primary reference. Nilsson *et al.* teaches general methods relating to fusion proteins, but does not disclose a library as defined by the present claims, and therefore fails to suggest the present invention.

The cited combination of references do not provide one of skill in the art with a reasonable expectation of success. In view of the above comments and amendments, withdrawal of the rejection is requested.

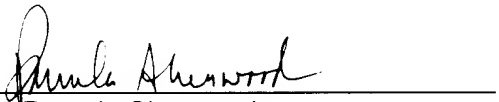
In view of the above remarks, this application is considered to be in good and proper form for allowance and the Examiner is respectfully requested to pass this application to issue.

If the Examiner finds that a Telephone Conference would expedite prosecution of this application, he is invited to contact the undersigned (650) 327-3400.

In the event that the transmittal letter is separated from this document and the Patent Office determines that extensions or other relief is required and/or fees are due applicants, the Applicant petitions for any required relief, including extensions of time, and authorize the Commissioner to charge our Deposit Account No. 50-0815, Order Number RIGL-004DIV, for any fees due in connection with the filing of this document. The Patent Office is not authorized to charge issue fees to our Deposit Account.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: January 27, 2003

By: 
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APPENDIX

VERSION WITH MARKINGS TO SHOW CHANGES MADE

Cancel claims 22 and 29.

16. (amended) A molecular library comprising at least 10^4 different retroviral nucleic acid sequences, wherein said retroviral nucleic acid sequences comprise an insertion of a nucleic acid sequence that encodes a candidate bioactive peptide of from 4 to 100 amino acids in length, wherein said candidate bioactive peptide comprises a randomized portion [of retroviruses comprising retroviral constructs, each construct comprising a randomized nucleic acid encoding a randomized peptide, wherein said library comprise at least 10^4 different randomized nucleic acids] .

17. (amended) A molecular library of retroviruses according to claim 16 comprising at least 10^5 different [randomized nucleic acids encoding a plurality of randomized peptides] retroviral nucleic acid sequences.

18. (amended) A molecular library of retroviruses according to claim 16 comprising at least 10^6 different [randomized nucleic acids encoding a plurality of randomized peptides] retroviral nucleic acid sequences.

19. (amended) A molecular library of retroviruses according to claim 16 comprising at least 10^7 different [randomized nucleic acids encoding a plurality of randomized peptides] retroviral nucleic acid sequences.

20. (amended) A molecular library of retroviruses according to claim 16 comprising at least 10^8 different [randomized nucleic acids encoding a plurality of randomized peptides] retroviral nucleic acid sequences.

21. (amended) A cellular library comprising at least 10^4 [of] mammalian cells [containing a molecular library of retroviral constructs, each construct comprising a randomized nucleic acid encoding a randomized peptide, wherein said molecular library comprises at least 10^4 different randomized nucleic acids] comprising different retroviral nucleic acid sequences, wherein said retroviral nucleic acid sequences comprise an insertion of a nucleic acid sequence that encodes a candidate bioactive peptide of from 4 to 100 amino acids in length, wherein said candidate bioactive peptide comprises a randomized portion.

23. (amended) [A] The molecular library [of retroviruses] comprising at least 10^4 different retroviral nucleic acid sequences according to claim 16, wherein said retroviral nucleic [acids] acid sequences further encode a fusion partner translationally fused to said nucleic acid sequence that encodes a candidate bioactive peptide.

24. (amended) [A] The molecular library [of retroviruses] comprising at least 10^4 different retroviral nucleic acid sequences according to claim 23, wherein said fusion partner comprises a targeting sequence.

25. (amended) [A] The molecular library [of retroviruses] comprising at least 10^4 different retroviral nucleic acid sequences according to claim 23, wherein said fusion partner comprises a rescue sequence.

26. (amended) [A] The molecular library [of retroviruses] comprising at least 10^4 different retroviral nucleic acid sequences according to claim 23, wherein said fusion partner comprises a stability sequence.

27. (amended) [A] The molecular library [of retroviruses] comprising at least 10^4 different retroviral nucleic acid sequences according to claim 23, wherein said fusion partner comprises a dimerization sequence.

28. (amended) [A The molecular library [of retroviruses] comprising at least 10^4 different retroviral nucleic acid sequences according to claim 16, wherein said randomized [nucleic acids are] portion is biased in [their] randomization.

30. (amended) A cellular library comprising at least 10^4 [of] mammalian cells [containing a molecular library of retroviral constructs, said library of cells intracellularly expressing at least 10^4 randomized peptides, wherein said each of said peptides is linked to a fusion partner] comprising different retroviral nucleic acid sequences, wherein said retroviral nucleic acid sequences comprise an insertion of a nucleic acid sequence that encodes a candidate bioactive peptide of from 4 to 100 amino acids in length translationally fused to a fusion partner, wherein said candidate bioactive peptide comprises a randomized portion, and said candidate bioactive peptide is intracellular.

31. (amended) [A] The cellular library according to Claim 30, wherein said fusion partner comprises a rescue sequence.